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The not so innocent bystander: an unusual cause of progressive breathlessness

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SUMMARY

This case report discusses a 76 year old gentleman who presented with symptomatic diffuse alveolar-septal and trachea-bronchial amyloidosis with a low grade monoclonal gammopathy.

This patient had a combination of both symptomatic diffuse alveolar-septal interstitial disease and trachea-bronchial amyloidosis, features that contradict the widely accepted presentations seen in this disease. Firstly, trachea-bronchial amyloidosis has only ever been documented as localised disease without systemic involvement. Secondly, diffuse alveolar-septal interstitial disease is rarely identified with clinical symptoms unless there is significant cardiac involvement.

This case highlights a number learning points in the diagnosis and management of systemic AL amyloidosis. 1) There is a need for a high index of suspicion for diagnosis due to the potential subtlety of a plasma cell clone underlying AL amyloidosis, requiring serum free light chain assays to increase sensitivity. 2) Haematological response and recovery of organ dysfunction is not a linear relationship due to the slower reversal of amyloid deposition; therefore, ongoing monitoring is required to identify those in need of repeated therapy. However, haematological response is a marker of overall survival. 3) Multisystem assessment and multidisciplinary collaboration are critical in optimising the care of patients with systemic AL amyloidosis.

Max Lyon (ML – Foundation Year 2 doctor)

A 76-year-old retired office worker was referred to the respiratory clinic with an 18 month history of progressive breathlessness and dry cough. He denied diurnal variation, paroxysmal nocturnal dyspnoea, orthopnoea, ankle swelling, or constitutional symptoms. He denied any environmental exposures, acid reflux or connective tissue disease symptoms. He was an ex-smoker with a 10 pack-year history. He had a past medical history of hypertension and hypercholesterolaemia for which he was taking Simvastatin and Ramipril. He had recently received (2 months previously) hormone injections and local radiotherapy for a concurrent diagnosis of prostate carcinoma.

His vital signs were normal. Bi-basal fine inspiratory crepitations were audible on auscultation. Cardiovascular examination was normal. Lung function tests revealed an obstructive pattern with significantly reduced gas transfer (Figure 1A).

Chest X-ray demonstrated reticular nodular opacification throughout both lung fields, with areas of consolidation at both lung bases (Figure 1B). High resolution CT thorax (HRCT) showed diffuse perilymphatic micronodules and interlobular septal thickening through the upper zones combined with conglomerate basal opacification, containing elements of calcification (Figure 1C, D). The stomach was diffusely thickened. Transthoracic echocardiogram revealed preserved left ventricular systolic function, with normal right heart and function. There was very mild tricuspid regurgitation with a right ventricular systolic pressure of 41mmHg, suggesting mildly raised pulmonary artery pressure.

Dr Mike Darby, Radiology Consultant

The differential diagnosis of interstitial lung disease presenting in a 76-year-old gentleman is broad and includes, hypersensitivity pneumonitis, connective tissue disease-associated ILD (CTD-ILD) and the idiopathic interstitial pneumonias, particularly idiopathic pulmonary fibrosis, but in this case none of the features were compatible with these diagnoses.

The presence of calcification raises the possibility of pneumoconiosis such as silicosis, but there were no relevant occupational or drug exposures and the distribution of calcification very atypical. Sarcoidosis is a consideration given the peri-lymphatic distribution of nodules, whilst lymphangitis carcinomatosa is also a consideration given the combination of alveolar septal thickening and perilymphatic micronodules, but, again calcification is very atypical.

A bone scan with single photon computed tomography performed as part of the staging investigations for his prostatic carcinoma (not shown), revealed uptake in the lung bases, suggesting

the deposition of calcium was by an osteoblastic process, raising amyloidosis as a further differential.

Abdominal CT also showed marked thickening and distortion of the stomach, which also raised the possibility of amyloid infiltration.

ML

Given the wide differential, a thorough diagnostic work up was required and a multidisciplinary team approach essential. CT guided lung biopsy and VATS lung biopsy were considered too high risk, taking into consideration the CT appearances, co-morbidities, lung function and patient wishes.

An upper gastro-intestinal endoscopy was performed to further evaluate the abnormalities identified on CT.

Whilst macroscopically the appearances of the oesophagus and gastric mucosa were normal, biopsies demonstrated a mild chronic inflammatory cell infiltrate within the lamina propria and hyalinised amorphous paucicellular tissue that required further histological evaluation. The amorphous material within the submucosa stained with Congo red and displayed apple-green birefringence when viewed under high intensity cross-polarised light (Figure 1E, F), the classical appearances of amyloid.

Dr Shaney L Barratt (Consultant Respiratory Physician)

Amyloidosis arises from heterogeneous diseases characterised by tissue deposition of an abnormal fibrillary protein with serum amyloid P component and other glycoproteins. The abnormal protein forms the bulk of deposits and these may cause organ dysfunction and eventually death [1]. They can be classified according to 1) the abnormal misfolded precursor protein, 2) major organ involvement and/or 3) whether the disease is localised or systemic.

Congo red staining that produces green birefringence under cross polarised light remains the gold standard for histological confirmation of the diagnosis of amyloid. Typing of amyloid fibrils using immunohistochemistry or mass spectrometry is a crucial next step as it informs exploration and treatment pathways; only systemic immunoglobulin AL amyloidosis is treated with chemotherapy or stem cell transplantation [1].

Immunohistochemical staining of the amyloid deposits was performed using monospecific antibodies reactive with serum amyloid A protein (SAA), transthyretin (TTR), kappa (κ) and lambda (λ) immunoglobulin light chains. The amyloid deposits stained with antibodies to λ chains, confirming amyloid of the AL (immunoglobulin light chain) subtype.

SLB

The presence of AL fibrils raised the suspicion of systemic disease with at least pulmonary and gastric involvement. Full assessment of the burden of disease was crucial to guide treatment strategy and enable prognostication and so is best co-ordinated through specialist centres.

Several clinical features of systemic amyloidosis; namely macroglossia, periorbital purpura, nephrotic range proteinuria, heart failure with preserved ejection fraction, non-diabetic peripheral neuropathy, unexplained hepatomegaly, or diarrhoea, were notably absent [1]. Baseline cardiac (N-terminal pro-brain natriuretic peptide, electrocardiogram, transthoracic echocardiogram, cardiac MRI), renal (urine protein/creatinine ratio, estimated glomerular filtration rate) and liver function investigations were all normal. He was referred to the NHS National Amyloidosis Centre where serum amyloid P component scintigraphy did not identify any additional visceral involvement.

AL associated disease is the most frequently described subtype of systemic amyloid, accounting for approximately 70% cases, with the vast majority having low grade and otherwise benign monoclonal gammopathies [1]. Concerns were therefore raised with regards to an underlying monoclonal gammopathy or haematological malignancy.

Serum and urinary protein electrophoresis with immunofixation, serum free light chain (FLC) assay for κ and λ immunoglobulin light chains and bone marrow aspiration/biopsy were performed.

Dr Whiteway (Consultant Haematologist)

Diagnosing AL amyloidosis requires proving systemic amyloid deposition, typing the deposits, assessing the nature of monoclonal disease and assessment of the degree of system disease to provide staging and prognostic information. Serum protein electrophoresis was normal, immunofixation band of a small IgD λ monoclonal protein and monoclonal λ free light chains, and immunoglobulin levels were within reference ranges. Serum free light chain assay showed excess λ light chains of 255.8 mg/L (5.7-26.3mg/l) with κ / λ ratio 0.12. Bone marrow assessment was consistent with a monoclonal gammopathy, and suggestive of amyloid in vessel walls. A diagnosis of systemic AL amyloidosis revised Mayo stage I, with presumed lung involvement was made.

Treatment for systemic AL amyloidosis is intended to reduce the excess free light chain load and thereby reverse amyloid deposition. Chemotherapy appropriate to the disorder producing abnormal FLC is used, as in this case where a combination of cyclophosphamide, bortezomib (a proteasome inhibitor), dexamethasone treatment regime (CyBorDex) was chosen. A complete haematological response was achieved after 2 of the 4 cycles given (Figure 1G). Consolidation with high dose

chemotherapy and autologous haemopoietic stem cell transplantation was considered to carry an unacceptable risk of morbidity.

ML

Shortly after completing his fourth cycle of chemotherapy, he developed recurrent, small volume haemoptysis. Repeat CT reported no active change whilst excluding the presence of pulmonary emboli or bronchial artery hypertrophy.

A bronchoscopy demonstrated multiple small volume nodules throughout the tracheobronchial tree with the appearances of diffuse abnormal infiltration with pin-point bleeding (Figure 1H).

Dr Nidhi Bhatt (Consultant Pathologist) NB

Endobronchial biopsies demonstrated a mildly inflamed bronchial mucosa and a mild eosinophilic subepithelial infiltrate that stained positive for Congo red with birefringence on polarised light (Figure 1I, J,K).

SLB

Pathologically, amyloidosis can be present as three main patterns in the lung; tracheobronchial, nodular pulmonary and diffuse alveolar-septal interstitial disease but rarely dominates the clinical picture.

Tracheobronchial and nodular patterns are mostly seen in localised disease without clonal proliferation. A case study of the Mayo clinic experience between 1973-1999, identified only 17 cases of tracheobronchial amyloidosis, all with localised disease [2].

Diffuse alveolar septal amyloidosis is usually a manifestation of systemic, multi-organ disease, most commonly identified histopathologically in post-mortem samples [3]. Clinically apparent diffuse alveolar septal disease is extremely rare. Among 474 cases of AL amyloidosis presenting to the Mayo clinic between 1981 and 1992, no symptomatic pulmonary presentations were reported [4]. Authors have thus postulated that the histologic and clinical pulmonary disease in AL patients were principal markers of severe cardiac infiltration, something that our particular case would not support[5].

To our knowledge, the clinical presentation of such extensive alveolar-septal disease in combination with clinically apparent tracheobronchial disease is unique. Whilst the absence of any notable cardiac involvement in combination with this pulmonary pathology is another finding that is equally rare, highlighting the variability in the presentation and pathology of this disease.

Key learning points:

1) A high index of suspicion is required for diagnosis; a plasma cell clone underlying AL amyloidosis may be subtle and not detected by serum protein electrophoresis and immunofixation of serum and urine. Serum free light chain assays increase diagnostic sensitivity.

2) Assessment for AL amyloidosis requires multisystem investigation and multidisciplinary collaboration.

3) Haematological response and response in organ dysfunction can be asynchronous because reversal of amyloid deposition is slow, although haematological response is a marker of overall survival. Ongoing monitoring is required, and therapy may need to be repeated.

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Conflicting Interests

There are no conflicting interests to declare.

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Appendix

Figure 1

See attachment